Fig. 1A

```
     1S   10    15   20    25   30    35   40    45   50    55   60    65   70
GAATTCGGCA CGAGCAAACA GTCATTAGTG GACGACTCTA TTGTAATAAA CTGTGCTTTA AAATGTAAAC

     75   80    85   90    95  100   105  110   115  120   125  130   135
CAGGGAGCGT TTTTTTCCCT CACATTGTCC AGAAGCAACC TTTCTTCCTG AGCCTGGATT AATC ATG
                                                                    M>

    140   145   150   155   160   165   170   175   180   185   190
AGA GAG CTC GTC AAC ATT CCA CTG TTA CAG ATG CTC ACC CTG GTT GCC TTC AGC GGG
 R   E   L   V   N   I   P   L   L   Q   M   L   T   L   V   A   F   S   G>

195   200   205   210   215   220   225   230   235   240   245   250
ACC GAG AAA CTT CCA AAA GCC CCT GTC ATC ACC ACG CCT CTT GAA ACT GTA GAT GCC
 T   E   K   L   P   K   A   P   V   I   T   T   P   L   E   T   V   D   A>

    255   260   265   270   275   280   285   290   295   300   305
TTA GTT GAA GAA GTG GCG ACT TTC ATG TGC GCC GTG GAA TCC TAC CCT CAG CCT GAA
 L   V   E   E   V   A   T   F   M   C   A   V   E   S   Y   P   Q   P   E>

310   315   320   325   330   335   340   345   350   355   360   365
ATT TCT TGG ACC AGA AAT AAA ATT CTC ATC AAG CTG TTT GAC ACC CGC TAC AGC ATC
 I   S   W   T   R   N   K   I   L   I   K   L   F   D   T   R   Y   S   I>

    370   375   380   385   390   395   400   405   410   415   420
CGA GAG AAC GGT CAG CTC CTC ACC ATC CTG AGT GTG GAG GAC AGT GAT GAT GGC ATC
 R   E   N   G   Q   L   L   T   I   L   S   V   E   D   S   D   D   G   I>

425   430   435   440   445   450   455   460   465   470   475
TAC TGC TGC ACA GCC AAC AAT GGA GTG GGA GGA GCG GTG GAA AGT TGT GGC GCC CTG
 Y   C   C   T   A   N   N   G   V   G   G   A   V   E   S   C   G   A   L>

480   485   490   495   500   505   510   515   520   525   530   535
CAA GTG AAG ATG AAG CCT AAA ATA ACT CGT CCT CCC ATC AAT GTA AAA ATA ATT GAG
 Q   V   K   M   K   P   K   I   T   R   P   P   I   N   V   K   I   I   E>

    540   545   550   555   560   565   570   575   580   585   590
GGA TTG AAA GCA GTC CTA CCG TGC ACT ACG ATG GGT AAC CCC AAG CCA TCC GTG TCC
 G   L   K   A   V   L   P   C   T   T   M   G   N   P   K   P   S   V   S>

595   600   605   610   615   620   625   630   635   640   645   650
TGG ATT AAG GGG GAC AGT GCT CTC AGG GAA AAT TCC AGG ATT GCA GTT CTT GAA TCT
 W   I   K   G   D   S   A   L   R   E   N   S   R   I   A   V   L   E   S>

    655   660   665   670   675   680   685   690   695   700   705
GGG AGT TTA AGG ATC CAT AAT GTG CAA AAG GAA GAC GCA GGA CAG TAC CGA TGT GTG
 G   S   L   R   I   H   N   V   Q   K   E   D   A   G   Q   Y   R   C   V>

710   715   720   725   730   735   740   745   750   755   760
GCA AAA AAC AGC CTG GGC ACA GCT TAC TCC AAA CTG GTG AAG CTG GAA GTG GAG GTT
 A   K   N   S   L   G   T   A   Y   S   K   L   V   K   L   E   V   E   V>

765   770   775   780   785   790   795   800   805   810   815   820
TTT GCA AGA ATC CTG CGT GCT CCT GAA TCC CAC AAT GTC ACC TTT GGT TCC TTT GTA
 F   A   R   I   L   R   A   P   E   S   H   N   V   T   F   G   S   F   V>
```

Fig. 1B

```
 825  830  835  840  845  850  855  860  865  870  875
ACC CTA CGC TGC ACA GCA ATA GGC ATG CCT GTC CCC ACC ATC AGC TGG ATT GAA AAC
 T   L   R   C   T   A   I   G   M   P   V   P   T   I   S   W   I   E   N>

 880  885  890  895  900  905  910  915  920  925  930  935
GGA AAT GCT GTT TCT TCA GGT TCC ATT CAA GAG AAT GTG AAA GAC CGA GTG ATT GAC
 G   N   A   V   S   S   G   S   I   Q   E   N   V   K   D   R   V   I   D>

 940  945  950  955  960  965  970  975  980  985  990
TCA AGA CTC CAG CTC TTT ATC ACA AAG CCA GGA CTC TAC ACA TGC ATA GCT ACC AAT
 S   R   L   Q   L   F   I   T   K   P   G   L   Y   T   C   I   A   T   N>

 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045
AAG CAT GGA GAG AAA TTC AGT ACC GCA AAG GCT GCA GCC ACT GTC AGT ATA GCA GAA
 K   H   G   E   K   F   S   T   A   K   A   A   A   T   V   S   I   A   E>

1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105
TGG AGC AAA TCA CAG AAA GAA AGC AAA GGC TAC TGT GCC CAG TAC AGA GGG GAG GTG
 W   S   K   S   Q   K   E   S   K   G   Y   C   A   Q   Y   R   G   E   V>

1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160
TGT GAT GCC GTC CTG GTG AAA GAC TCT CTT GTC TTC TTC AAC ACC TCC TAT CCC GAC
 C   D   A   V   L   V   K   D   S   L   V   F   F   N   T   S   Y   P   D>

1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220
CCT GAG GAG GCC CAA GAG CTG CTG ATC CAC ACT GCG TGG AAT GAA CTC AAG GCT GTG
 P   E   E   A   Q   E   L   L   I   H   T   A   W   N   E   L   K   A   V>

1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275
AGC CCA CTC TGC CGA CCA GCT GCC GAG GCT CTG CTG TGT AAT CAC CTC TTC CAG GAG
 S   P   L   C   R   P   A   A   E   A   L   L   C   N   H   L   F   Q   E>

1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330
TGC AGC CCT GGA GTG CTA CCT ACT CCT ATG CCC ATT TGC AGA GAG TAC TGC TTG GCA
 C   S   P   G   V   L   P   T   P   M   P   I   C   R   E   Y   C   L   A>

1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390
GTA AAG GAG CTC TTC TGT GCA AAG GAA TGG CTG GCA ATG GAA GGG AAG ACC CAC CGC
 V   K   E   L   F   C   A   K   E   W   L   A   M   E   G   K   T   H   R>

1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445
GGA CTC TAC AGA TCC GGG ATG CAT TTC CTC CCG GTC CCG GAG TGC AGC AAG CTT CCC
 G   L   Y   R   S   G   M   H   F   L   P   V   P   E   C   S   K   L   P>

1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505
AGC ATG CAC CAG GAC CCC ACA GCC TGC ACA AGA-CTG CCG TAT TTA GAT TAT AAA AAA
 S   M   H   Q   D   P   T   A   C   T   R   L   P   Y   L   D   Y   K   K>

1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560
GAA AAC ATA ACA ACA TTC CCG TCC ATA ACG TCC TCC AAG CCG AGC GTG GAC ATT CCA
 E   N   I   T   T   F   P   S   I   T   S   S   K   P   S   V   D   I   P>

1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615
AAC CTG CCT GCC TCC ACG TCT TCC TTC GCC GTC TCG CCT GCG TAC TCC ATG ACT GTC
 N   L   P   A   S   T   S   S   F   A   V   S   P   A   Y   S   M   T   V>
```

Fig. 1C

```
1620  1625  1630  1635  1640  1645  1650  1655  1660  1665  1670  1675
ATC ATC TCC ATC ATG TCC TGC TTT GCG GTG TTT GCT CTC CTC ACC ATC ACT ACT CTC
 I   I   S   I   M   S   C   F   A   V   F   A   L   L   T   I   T   T   L>

1680  1685  1690  1695  1700  1705  1710  1715  1720  1725  1730
TAT TGC TGC CGA AGG AGG AGA GAG TGG AAA AAT AAG AAA AGA GAG TCG GCA GCG GTG
 Y   C   C   R   R   R   R   E   W   K   N   K   K   R   E   S   A   A   V>

1735  1740  1745  1750  1755  1760  1765  1770  1775  1780  1785  1790
ACC CTC ACC ACA TTG CCT TCC GAG CTC CTG CTG GAC AGG CTG CAT CCC AAC CCC ATG
 T   L   T   T   L   P   S   E   L   L   L   D   R   L   H   P   N   P   M>

1795  1800  1805  1810  1815  1820  1825  1830  1835  1840  1845
TAC CAG AGG ATG CCA CTC CTT CTG AAT CCC AAG TTG CTC AGC CTG GAG TAT CCG AGG
 Y   Q   R   M   P   L   L   L   N   P   K   L   L   S   L   E   Y   P   R>

1850  1855  1860  1865  1870  1875  1880  1885  1890  1895  1900
AAT AAC ATC GAG TAT GTC AGA GAC ATC GGA GAG GGA GCG TTT GGA AGG GTC TTT CAA
 N   N   I   E   Y   V   R   D   I   G   E   G   A   F   G   R   V   F   Q>

1905  1910  1915  1920  1925  1930  1935  1940  1945  1950  1955  1960
GCG AGG GCC CCA GGC TTG CTT CCT TAT GAA CCC TTC ACT ATG GTG GCT GTG AAG ATG
 A   R   A   P   G   L   L   P   Y   E   P   F   T   M   V   A   V   K   M>

1965  1970  1975  1980  1985  1990  1995  2000  2005  2010  2015
CTG AAG GAG GAG GCC TCC GCA GAT ATG CAG GCA GAC TTT CAG AGG GAG GCA GCC CTC
 L   K   E   E   A   S   A   D   M   Q   A   D   F   Q   R   E   A   A   L>

2020  2025  2030  2035  2040  2045  2050  2055  2060  2065  2070  2075
ATG GCG GAG TTT GAC AAC CCC AAC ATT GTG AAG CTC TTA GGT GTG TGT GCT GTT GGG
 M   A   E   F   D   N   P   N   I   V   K   L   L   G   V   C   A   V   G>

2080  2085  2090  2095  2100  2105  2110  2115  2120  2125  2130
AAG CCA ATG TGC CTG CTC TTT GAA TAT ATG GCC TAT GGT GAC CTC AAT GAG TTC CTC
 K   P   M   C   L   L   F   E   Y   M   A   Y   G   D   L   N   E   F   L>

2135  2140  2145  2150  2155  2160  2165  2170  2175  2180  2185
CGA AGC ATG TCC CCT CAC ACT GTG TGC AGC CTC AGC CAC AGT GAC CTG TCC ACG AGG
 R   S   M   S   P   H   T   V   C   S   L   S   H   S   D   L   S   T   R>

2190  2195  2200  2205  2210  2215  2220  2225  2230  2235  2240  2245
GCT CGG GTG TCC AGC CCT GGT CCT CCA CCC CTG TCT TGT GCG GAA CAG CTC TGT ATT
 A   R   V   S   S   P   G   P   P   P   L   S   C   A   E   Q   L   C   I>

2250  2255  2260  2265  2270  2275  2280  2285  2290  2295  2300
GCC AGG CAA GTG GCA GCT GGC ATG GCC TAC CTG TCG GAG CGC AAG TTT GTC CAT CGG
 A   R   Q   V   A   A   G   M   A   Y   L   S   E   R   K   F   V   H   R>

2305  2310  2315  2320  2325  2330  2335  2340  2345  2350  2355  2360
GAC TTA GCT ACC AGG AAC TGC CTG GTT GGA GAG AAC ATG GTG GTG AAA ATT GCA GAC
 D   L   A   T   R   N   C   L   V   G   E   N   M   V   V   K   I   A   D>

2365  2370  2375  2380  2385  2390  2395  2400  2405  2410  2415
TTT GGC CTC TCT AGG AAC ATC TAC TCC GCA GAC TAC TAC AAA GCT GAT GGA AAC GAT
 F   G   L   S   R   N   I   Y   S   A   D   Y   Y   K   A   D   G   N   D>
```

Fig. 1D

```
2420   2425   2430   2435   2440   2445   2450   2455   2460   2465   2470
 *      *      *      *      *      *      *      *      *      *      *
GCT ATA CCT ATC CGC TGG ATG CCA CCC GAG TCT ATC TTC TAC AAC CGC TAC ACC ACG
 A   I   P   I   R   W   M   P   P   E   S   I   F   Y   N   R   Y   T   T>

2475 2480   2485   2490 2495   2500   2505 2510   2515   2520 2525   2530
      *      *      *      *      *      *      *      *      *      *
GAG TCA GAT GTG TGG GCT TAT GGC GTG GTC CTC TGG GAG ATC TTC TCC TAT GGA CTG
 E   S   D   V   W   A   Y   G   V   V   L   W   E   I   F   S   Y   G   L>

 2535 2540   2545   2550 2555   2560   2565 2570   2575   2580 2585
       *      *      *      *      *      *      *      *      *
CAG CCC TAC TAT GGA ATG GCC CAT GAG GAG GTC ATT TAC TAT GTG AGA GAT GGT AAC
 Q   P   Y   Y   G   M   A   H   E   E   V   I   Y   Y   V   R   D   G   N>

2590   2595 2600   2605   2610 2615   2620   2625 2630   2635   2640 2645
 *      *      *      *      *      *      *      *      *      *
ATC CTT GCC TGC CCT GAG AAC TGT CCC TTG GAA CTG TAC AAC CTT ATG CGC CTA TGT
 I   L   A   C   P   E   N   C   P   L   E   L   Y   N   L   M   R   L   C>

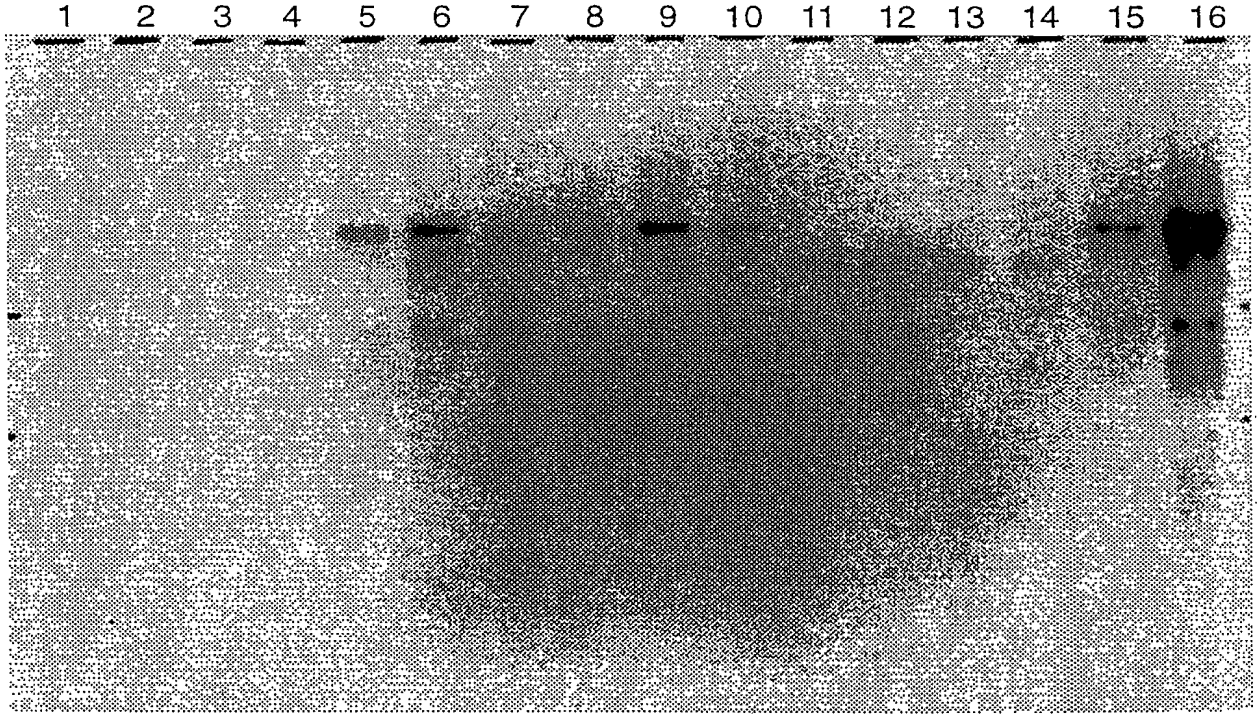
 2650   2655 2660   2665   2670 2675   2680   2685 2690   2695   2700
       *      *      *      *      *      *      *      *      *
TGG AGC AAG CTG CCT GCA GAC AGA CCC AGC TTC TGC AGT ATC CAC CGG ATC CTG CAG
 W   S   K   L   P   A   D   R   P   S   F   C   S   I   H   R   I   L   Q>

2705   2710   2715 2720   2725   2730 2735   2740   2745 2750   2755 2760
       *      *      *      *      *      *      *      *      *
CGC ATG TGC GAG AGA GCA GAG GGA ACG GTA GGC GTC TAA GGTTGACCA TGCTCAAACA
 R   M   C   E   R   A   E   G   T   V   G   V   *>

 2765 2770   2775 2780   2785 2790   2795 2800   2805 2810   2815 2820   2825 2830
       *      *      *      *      *      *      *      *      *      *
ACACCCAGGA GGATCTTTTC AGACTGCGAG CTGGAGGGAT CCTAAAGCAG AGGGCGNATA AGNNCAGATA

 2835 2840   2845 2850   2855 2860   2865
       *      *      *
GGAAGAGTTT ATCTCAGGCA GCACGTNCAG TTGGTTGTT
```

Fig.2.



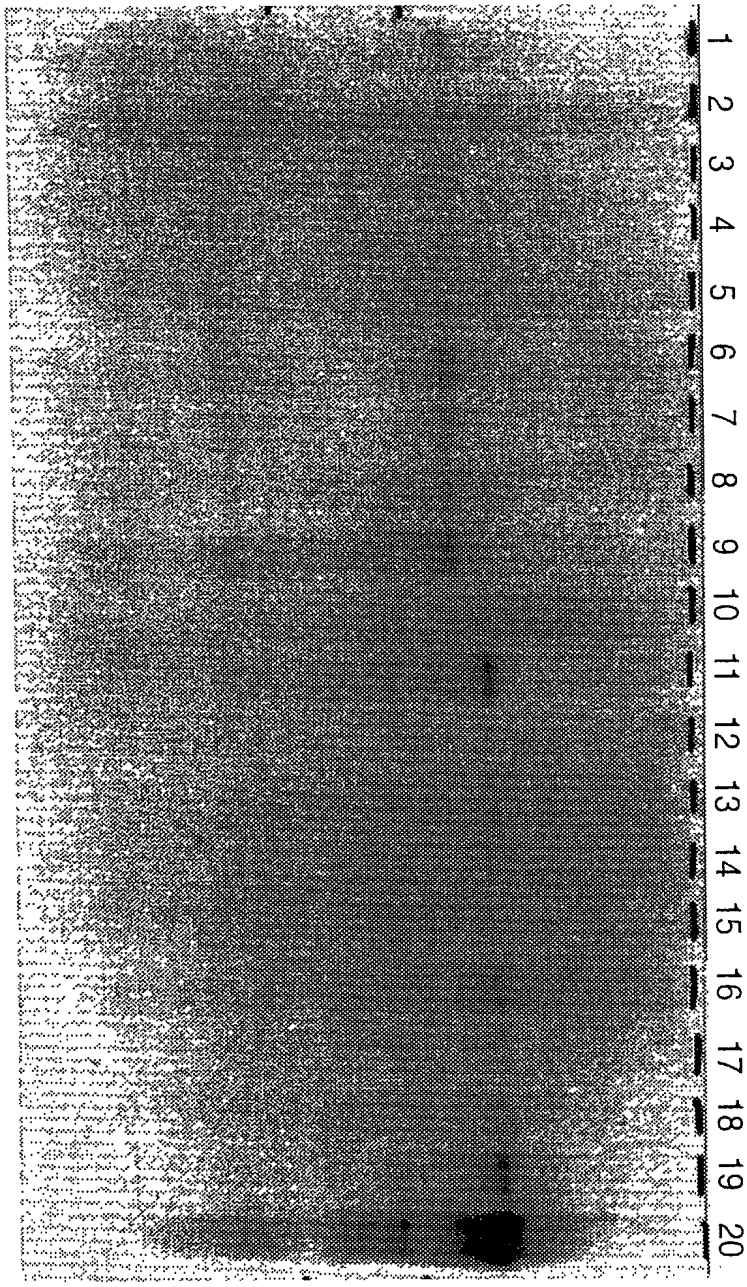


Fig.3.

Fig. 4A

```
          10         20         30         40         50         60
          *          *          *          *          *          *
ATG AGA GAG CTC GTC AAC ATT CCA CTG GTA CAT ATT CTT ACT CTG GTT GCC TTC AGC GGA
 M   R   E   L   V   N   I   P   L   V   H   I   L   T   L   V   A   F   S   G

          70         80         90        100        110        120
          *          *          *          *          *          *
ACT GAG AAA CTT CCA AAA GCT CCT GTC ATC ACC ACT CCT CTT GAA ACA GTG GAT GCC TTA
 T   E   K   L   P   K   A   P   V   I   T   T   P   L   E   T   V   D   A   L

         130        140        150        160        170        180
          *          *          *          *          *          *
GTT GAA GAA GTG GCT ACT TTC ATG TGT GCA GTG GAA TCC TAC CCC CAG CCT GAG ATT TCC
 V   E   E   V   A   T   F   M   C   A   V   E   S   Y   P   Q   P   E   I   S

         190        200        210        220        230        240
          *          *          *          *          *          *
TGG ACT AGA AAT AAA ATT CTC ATT AAA CTC TTT GAC ACC CCC TAC AGC ATC CGG GAG AAT
 W   T   R   N   K   I   L   I   K   L   F   D   T   R   Y   S   I   R   E   N

         250        260        270        280        290        300
          *          *          *          *          *          *
GGG CAG CTC CTC ACC ATC CTG AGT GTG GAA GAC AGT GAT GAT GGC ATT TAC TGC TGC ACG
 G   Q   L   L   T   I   L   S   V   E   D   S   D   D   G   I   Y   C   C   T

         310        320        330        340        350        360
          *          *          *          *          *          *
GCC AAC AAT GGT GTG GGA GGA GCT GTG GAG AGT TGT GGA GCC CTG CAA GTG AAG ATG AAA
 A   N   N   G   V   G   G   A   V   E   S   C   G   A   L   Q   V   K   M   K

         370        380        390        400        410        420
          *          *          *          *          *          *
CCT AAA ATA ACT CGC CCT CCC ATA AAT GTG AAA ATA ATA GAG GGA TTA AAA GCA GTC CTA
 P   K   I   T   R   P   P   I   N   V   K   I   I   E   G   L   K   A   V   L

         430        440        450        460        470        480
          *          *          *          *          *          *
CCA TGT ACT ACA ATG GGT AAT CCC AAA CCA TCA GTG TCT TGG ATA AAG GGA GAC AGC CCT
 P   C   T   T   M   G   N   P   K   P   S   V   S   W   I   K   G   D   S   P

         490        500        510        520        530        540
          *          *          *          *          *          *
CTC AGG GAA AAT TCC CGA ATT GCA GTT CTT GAA TCT GGG AGC TTG AGG ATT CAT AAC GTA
 L   R   E   N   S   R   I   A   V   L   E   S   G   S   L   R   I   H   N   V

         550        560        570        580        590        600
          *          *          *          *          *          *
CAA AAG GAA GAT GCA GGA CAG TAT CGA TGT GTG GCA AAA AAC AGC CTC GGG ACA GCA TAT
 Q   K   E   D   A   G   Q   Y   R   C   V   A   K   N   S   L   G   T   A   Y

         610        620        630        640        650        660
          *          *          *          *          *          *
TCC AAA GTG GTG AAG CTG GAA GTT GAG GTT TTT GCC AGG ATC CTG CGG GCT CCT GAA TCC
 S   K   V   V   K   L   E   V   E   V   F   A   R   I   L   R   A   P   E   S

         670        680        690        700        710        720
          *          *          *          *          *          *
CAC AAT GTC ACC TTT GGC TCC TTT GTG ACC CTG CAC TGT ACA GCA ACA GGC ATT CCT GTC
 H   N   V   T   F   G   S   F   V   T   L   H   C   T   A   T   G   I   P   V
```

Fig. 4B

```
          730         740         750         760         770         780
          *           *           *           *           *           *
CCC ACC ATC ACC TGG ATT GAA AAC GGA AAT GCT GTT TCT TCT GGG TCC ATT CAA GAG AGT
 P   T   I   T   W   I   E   N   G   N   A   V   S   S   G   S   I   Q   E   S

          790         800         810         820         830         840
          *           *           *           *           *           *
GTG AAA GAC CGA GTG ATT GAC TCA AGA CTG CAG CTG TTT ATC ACC AAG CCA GGA CTC TAC
 V   K   D   R   V   I   D   S   R   L   Q   L   F   I   T   K   P   G   L   Y

          850         860         870         880         890         900
          *           *           *           *           *           *
ACA TGC ATA GCT ACC AAT AAG CAT GGG GAG AAG TTC AGT ACT GCC AAG GCT GCA GCC ACC
 T   C   I   A   T   N   K   H   G   E   K   F   S   T   A   K   A   A   A   T

          910         920         930         940         950         960
          *           *           *           *           *           *
ATC AGC ATA GCA GAA TGG AGT AAA CCA CAG AAA GAT AAC AAA GGC TAC TGC GCC CAG TAC
 I   S   I   A   E   W   S   K   P   Q   K   D   N   K   G   Y   C   A   Q   Y

          970         980         990         1000        1010        1020
          *           *           *           *           *           *
AGA GGG GAG GTG TGT AAT GCA GTC CTG GCA AAA GAT GCT CTT GTT TTT CTC AAC ACC TCC
 R   G   E   V   C   N   A   V   L   A   K   D   A   L   V   F   L   N   T   S

          1030        1040        1050        1060        1070        1080
          *           *           *           *           *           *
TAT GCG GAC CCT GAG GAG GCC CAA GAG CTA CTG GTC CAC ACG GCC TGG AAT GAA CTG AAA
 Y   A   D   P   E   E   A   Q   E   L   L   V   H   T   A   W   N   E   L   K

          1090        1100        1110        1120        1130        1140
          *           *           *           *           *           *
GTA GTG AGC CCA GTC TGC CGG CCA GCT GCT GAG GCT TTG TTG TGT AAC CAC ATC TTC CAG
 V   V   S   P   V   C   R   P   A   A   E   A   L   L   C   N   H   I   F   Q

          1150        1160        1170        1180        1190        1200
          *           *           *           *           *           *
GAG TGC AGT CCT GGA GTA GTG CCT ACT CCT ATT CCC ATT TGC AGA GAG TAC TGC TTG GCA
 E   C   S   P   G   V   V   P   T   P   I   P   I   C   R   E   Y   C   L   A

          1210        1220        1230        1240        1250        1260
          *           *           *           *           *           *
GTA AAG GAG CTC TTC TGC GCA AAA GAA TGG CTG GTA ATG GAA GAG AAG ACC CAC AGA GGA
 V   K   E   L   F   C   A   K   E   W   L   V   M   E   E   K   T   H   R   G

          1270        1280        1290        1300        1310        1320
          *           *           *           *           *           *
CTC TAC AGA TCC GAG ATG CAT TTG CTG TCC GTG CCA GAA TGC AGC AAG CTT CCC AGC ATG
 L   Y   R   S   E   M   H   L   L   S   V   P   E   C   S   K   L   P   S   M

          1330        1340        1350        1360        1370        1380
          *           *           *           *           *           *
CAT TGG GAC CCC ACG GCC TGT GCC AGA CTG CCA CAT CTA GAT TAT AAC AAA GAA AAC CTA
 H   W   D   P   T   A   C   A   R   L   P   H   L   D   Y   N   K   E   N   L

          1390        1400        1410        1420        1430        1440
          *           *           *           *           *           *
AAA ACA TTC CCA CCA ATG ACG TCC TCA AAG CCA AGT GTG GAC ATT CCA AAT CTG CCT TCC
 K   T   F   P   P   M   T   S   S   K   P   S   V   D   I   P   N   L   P   S
```

Fig. 4C

```
          1450        1460        1470        1480        1490        1500
           *           *           *           *           *           *
TCC TCC TCT TCT TCC TTC TCT GTC TCA CCT ACA TAC TCC ATG ACT GTA ATA ATC TCC ATC
 S   S   S   S   S   F   S   V   S   P   T   Y   S   M   T   V   I   I   S   I

          1510        1520        1530        1540        1550        1560
           *           *           *           *           *           *
ATG TCC AGC TTT GCA ATA TTT GTG CTT CTT ACC ATA ACT ACT CTC TAT TGC TGC CGA AGA
 M   S   S   F   A   I   F   V   L   L   T   I   T   T   L   Y   C   C   R   R

          1570        1580        1590        1600        1610        1620
           *           *           *           *           *           *
AGA AAA CAA TGG AAA AAT AAG AAA AGA GAA TCA GCA GCA GTA ACC CTC ACC ACA CTG CCT
 R   K   Q   W   K   N   K   K   R   E   S   A   A   V   T   L   T   T   L   P

          1630        1640        1650        1660        1670        1680
           *           *           *           *           *           *
TCT GAG CTC TTA CTA GAT AGA CTT CAT CCC AAC CCC ATG TAC CAG AGG ATG CCG CTC CTT
 S   E   L   L   L   D   R   L   H   P   N   P   M   Y   Q   R   M   P   L   L

          1690        1700        1710        1720        1730        1740
           *           *           *           *           *           *
CTG AAC CCC AAA TTG CTC AGC CTG GAG TAT CCA AGG AAT AAC ATT GAA TAT GTG AGA GAC
 L   N   P   K   L   L   S   L   E   Y   P   R   N   N   I   E   Y   V   R   D

          1750        1760        1770        1780        1790        1800
           *           *           *           *           *           *
ATC GGA GAG GGA GCG TTT GGA AGG GTG TTT CAA GCA AGG GCA CCA GGC TTA CTT CCC TAT
 I   G   E   G   A   F   G   R   V   F   Q   A   R   A   P   G   L   L   P   Y

          1810        1820        1830        1840        1850        1860
           *           *           *           *           *           *
GAA CCT TTC ACT ATG GTG GCA GTA AAG ATG CTC AAA GAA GAA GCC TCG GCA GAT ATG CAA
 E   P   F   T   M   V   A   V   K   M   L   K   E   E   A   S   A   D   M   Q

          1870        1880        1890        1900        1910        1920
           *           *           *           *           *           *
GCG GAC TTT CAG AGG GAG GCA GCC CTC ATG GCA GAA TTT GAC AAC CCT AAC ATT GTG AAG
 A   D   F   Q   R   E   A   A   L   M   A   E   F   D   N   P   N   I   V   K

          1930        1940        1950        1960        1970        1980
           *           *           *           *           *           *
CTA TTA GGA GTG TGT GCT GTC GGG AAG CCA ATG TGC CTG CTC TTT GAA TAC ATG GCC TAT
 L   L   G   V   C   A   V   G   K   P   M   C   L   L   F   E   Y   M   A   Y

          1990        2000        2010        2020        2030        2040
           *           *           *           *           *           *
GGT GAC CTC AAT GAG TTC CTC CGC AGC ATG TCC CCT CAC ACC GTG TGC AGC CTC AGT CAC
 G   D   L   N   E   F   L   R   S   M   S   P   H   T   V   C   S   L   S   H

          2050        2060        2070        2080        2090        2100
           *           *           *           *           *           *
AGT GAC TTG TCT ATG AGG GCT CAG GTC TCC AGC CCT GGG CCC CCA CCC CTC TCC TGT GCT
 S   D   L   S   M   R   A   Q   V   S   S   P   G   P   P   P   L   S   C   A

          2110        2120        2130        2140        2150        2160
           *           *           *           *           *           *
GAG CAG CTT TGC ATT GCC AGG CAG GTG GCA GCT GGC ATG GCT TAC CTC TCA GAA CGT AAG
 E   Q   L   C   I   A   R   Q   V   A   A   G   M   A   Y   L   S   E   R   K
```

Fig. 4D

```
          2170        2180        2190        2200        2210        2220
            *           *           *           *           *           *
TTT GTT CAC CGA GAT TTA GCC ACC AGG AAC TGC CTG GTG GGC GAG AAC ATG GTG GTG AAA
 F   V   H   R   D   L   A   T   R   N   C   L   V   G   E   N   M   V   V   K

          2230        2240        2250        2260        2270        2280
            *           *           *           *           *           *
ATT GCC GAC TTT GGC CTC TCC AGG AAC ATC TAC TCA GCA GAC TAC TAC AAA GCT AAT GAA
 I   A   D   F   G   L   S   R   N   I   Y   S   A   D   Y   Y   K   A   N   E

          2290        2300        2310        2320        2330        2340
            *           *           *           *           *           *
AAC GAC GCT ATC CCT ATC CGT TGG ATG CCA CCA GAG TCC ATT TTT TAT AAC CGC TAC ACT
 N   D   A   I   P   I   R   W   M   P   P   E   S   I   F   Y   N   R   Y   T

          2350        2360        2370        2380        2390        2400
            *           *           *           *           *           *
ACA GAG TCT GAT GTG TGG GCC TAT GGC GTG GTC CTC TGG GAG ATC TTC TCC TAT GGC CTG
 T   E   S   D   V   W   A   Y   G   V   V   L   W   E   I   F   S   Y   G   L

          2410        2420        2430        2440        2450        2460
            *           *           *           *           *           *
CAG CCC TAC TAT GGG ATG GCC CAT GAG GAG GTC ATT TAC TAC GTG CGA GAT GGC AAC ATC
 Q   P   Y   Y   G   M   A   H   E   E   V   I   Y   Y   V   R   D   G   N   I

          2470        2480        2490        2500        2510        2520
            *           *           *           *           *           *
CTC TCC TGC CCT GAG AAC TGC CCC GTG GAG CTG TAC AAT CTC ATG CGT CTA TGT TGG AGC
 L   S   C   P   E   N   C   P   V   E   L   Y   N   L   M   R   L   C   W   S

          2530        2540        2550        2560        2570        2580
            *           *           *           *           *           *
AAG CTG CCT GCA GAC AGA CCC AGT TTC ACC AGT ATT CAC CGA ATT CTG GAA CGC ATG TGT
 K   L   P   A   D   R   P   S   F   T   S   I   H   R   I   L   E   R   M   C

          2590        2600        2610
            *           *           *
GAG AGG GCA GAG GGA ACT GTG AGT GTC TAA
 E   R   A   E   G   T   V   S   V   *
```

Fig.5.

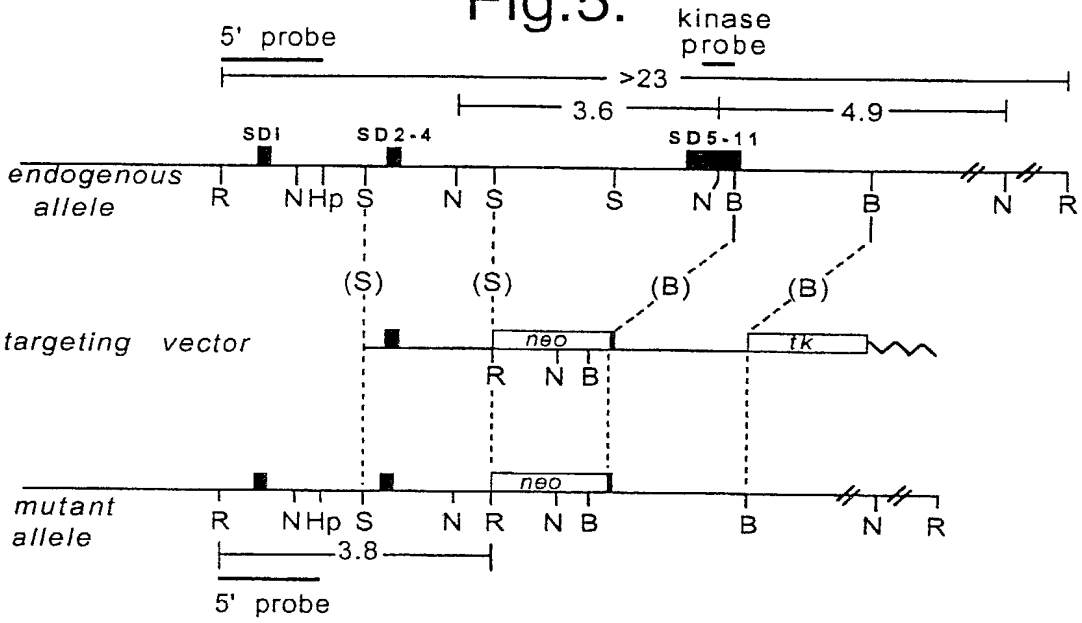

5' probe
kinase probe
>23
3.6
4.9
SD1
SD2-4
SD5-11
endogenous allele
R NHp S N S S N B B N R
(S) (S) (B) (B)
targeting vector
neo
tk
R N B
neo
mutant allele
R NHp S N R N B B N R
3.8
5' probe

Fig.6.

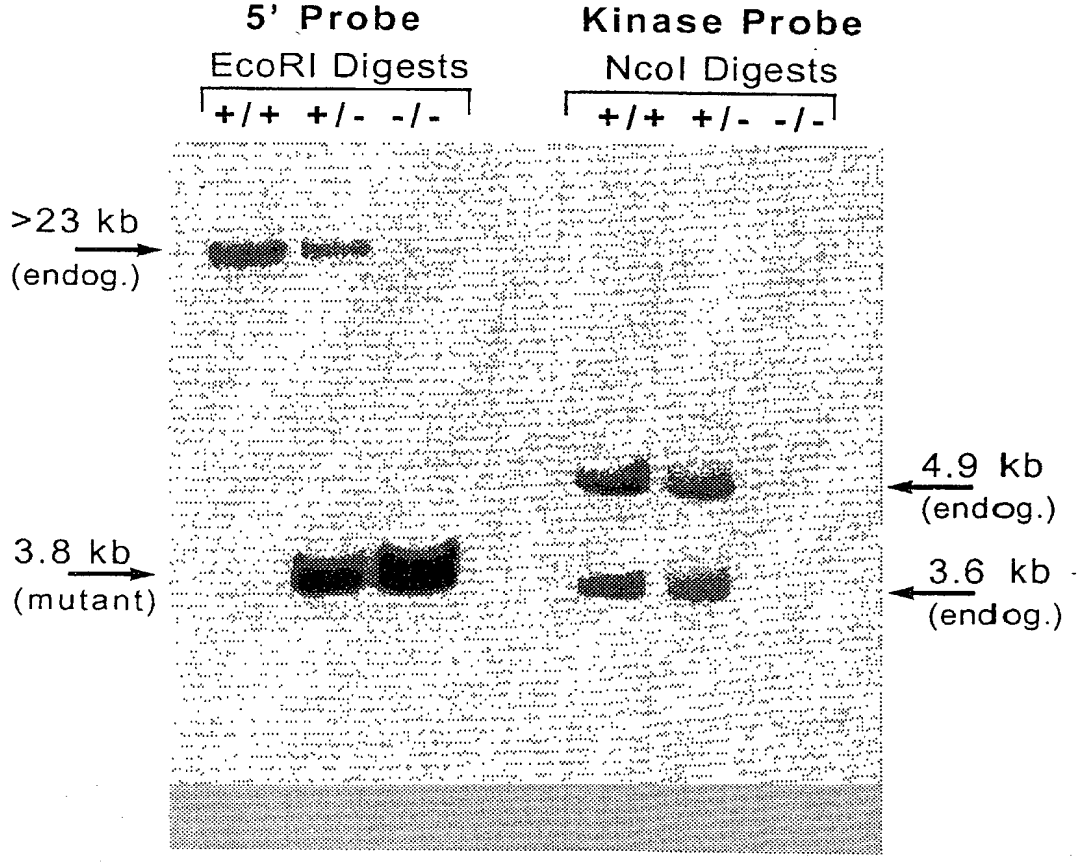

5' Probe
EcoRI Digests
+/+ +/- -/-
Kinase Probe
NcoI Digests
+/+ +/- -/-
>23 kb
(endog.)
4.9 kb
(endog.)
3.8 kb
(mutant)
3.6 kb
(endog.)

Fig.7A.

Fig.7B.

Fig.7C.

Fig.7D.

Fig.8A.

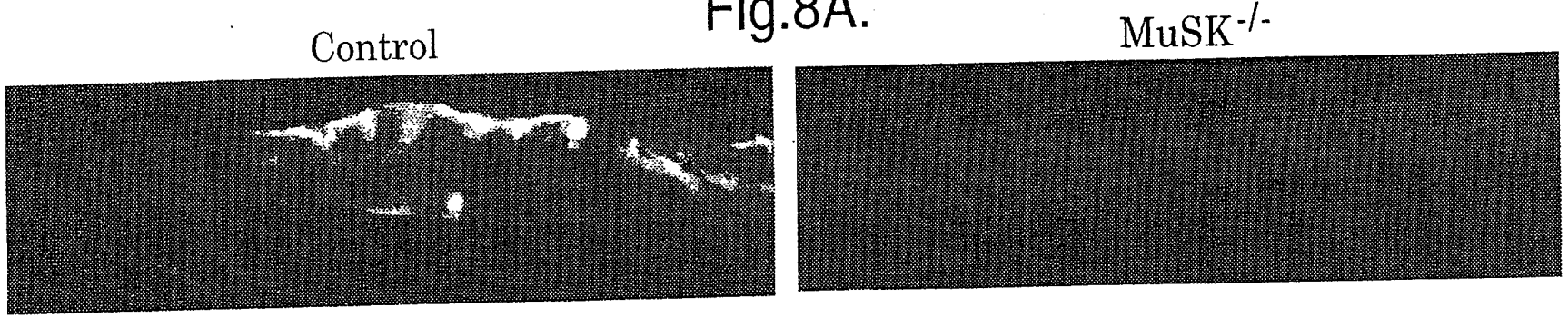


Fig.8B.

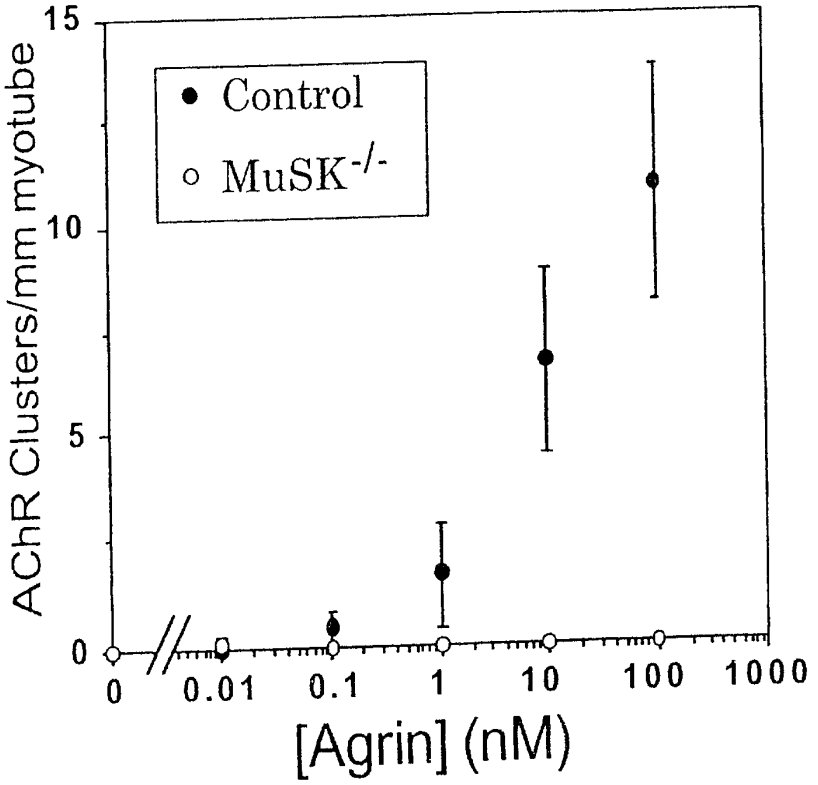


Fig.8C.

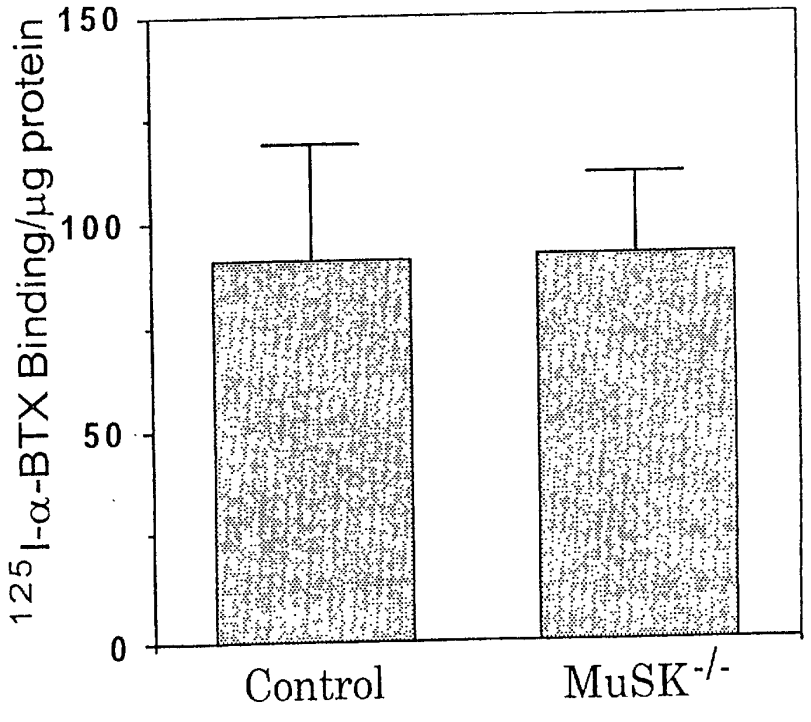


Fig.9A.

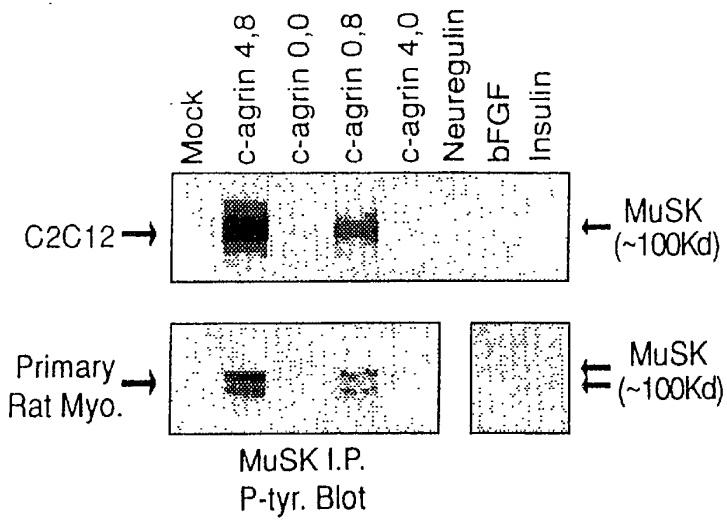


Fig.9B.

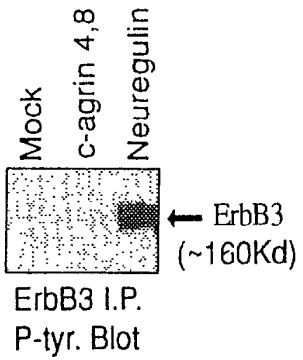


Fig.9C.

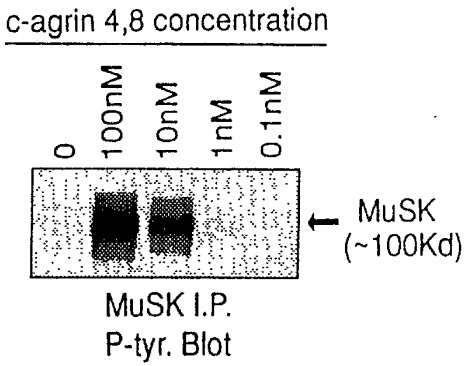


Fig.9D.

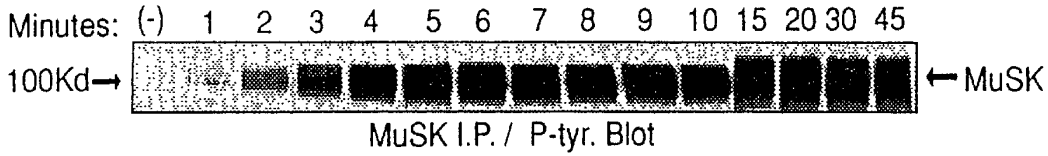


Fig.10A.

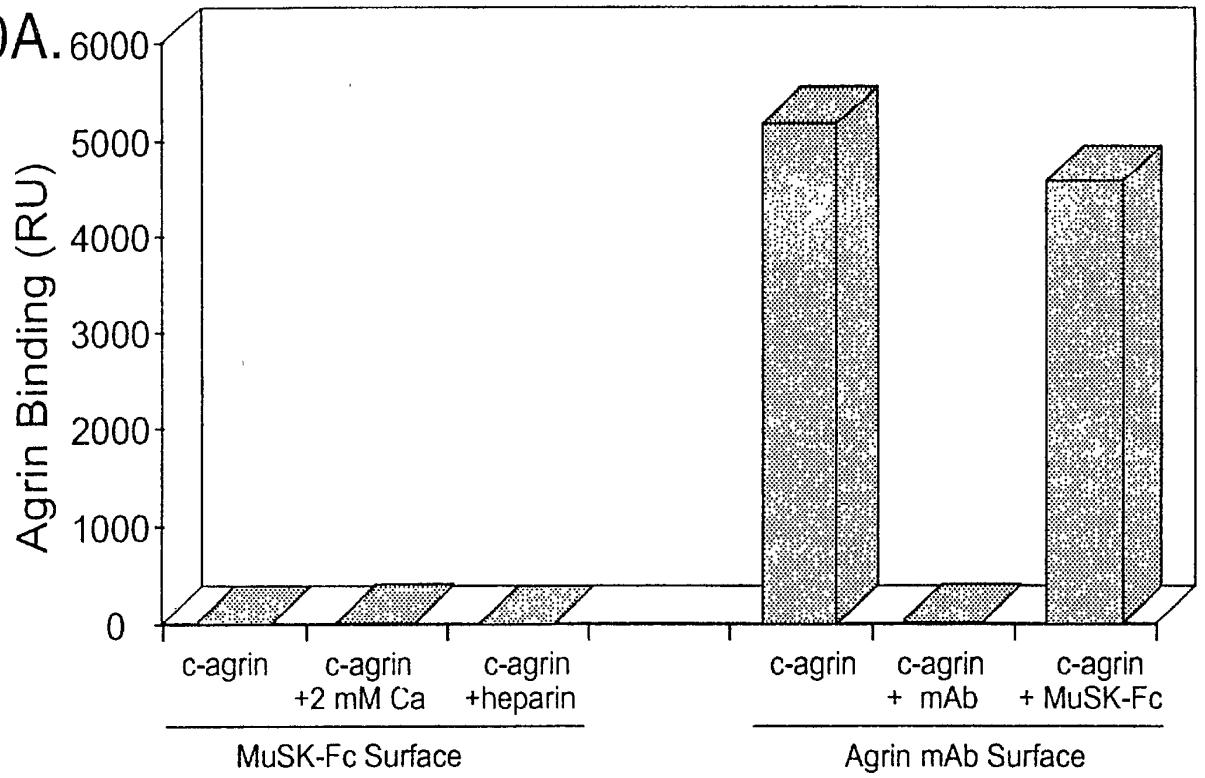


Fig.10B.

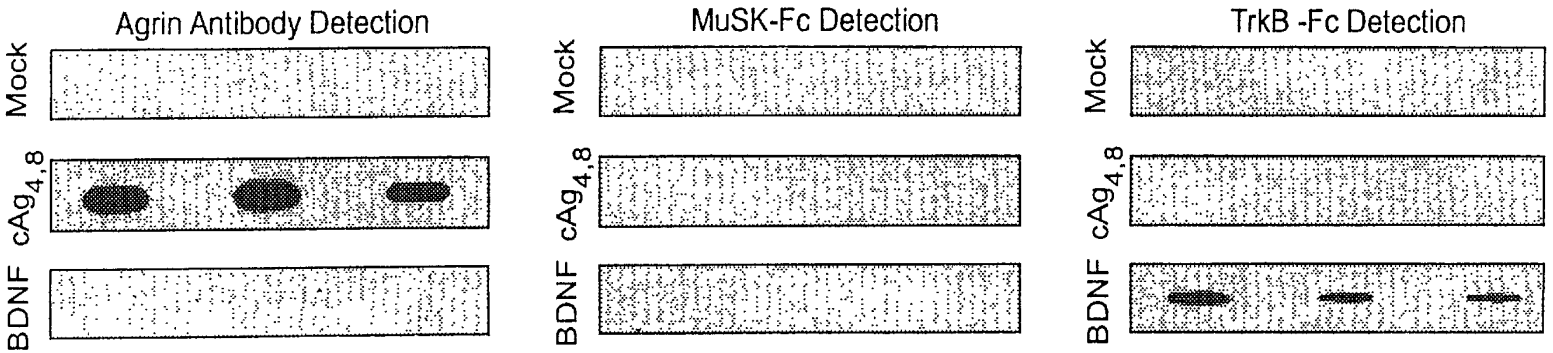


Fig.11.

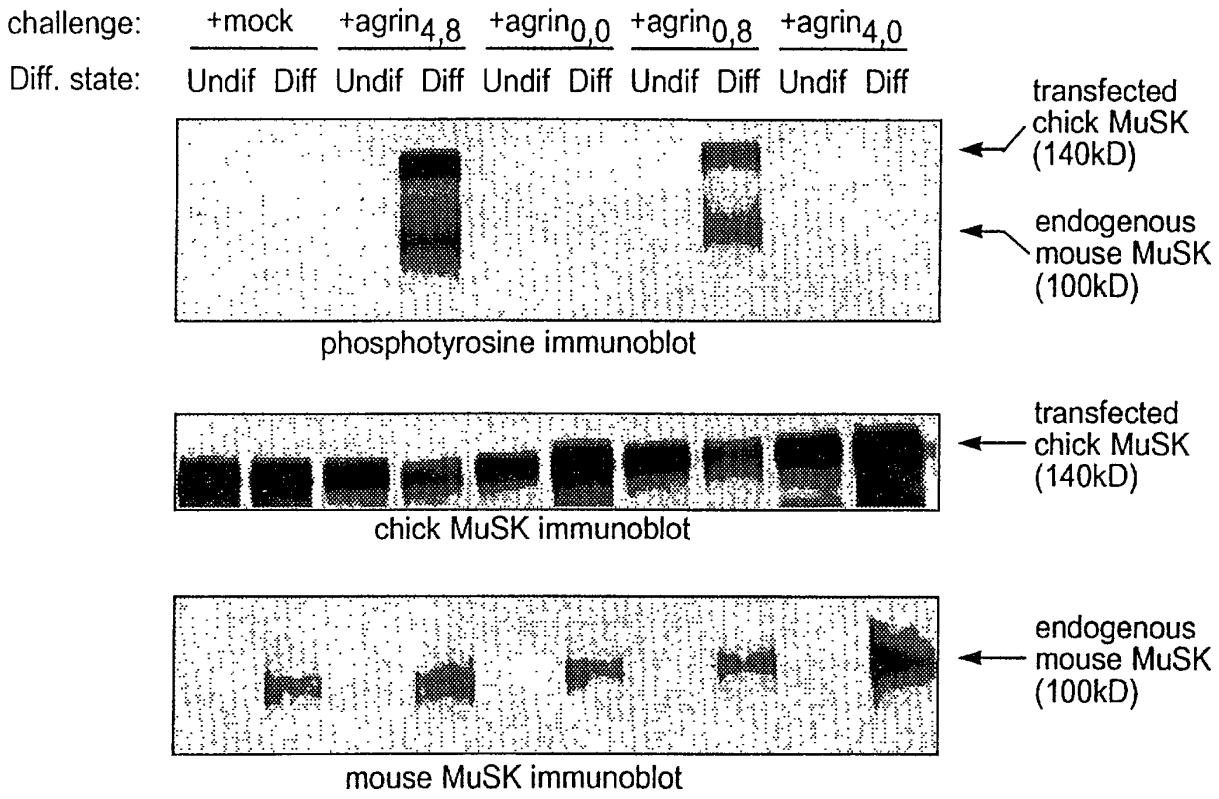

challenge:
+mock
+agrin4,8
+agrin0,0
+agrin0,8
+agrin4,0
Diff. state:
Undif Diff Undif Diff Undif Diff Undif Diff Undif Diff
transfected chick MuSK (140kD)
endogenous mouse MuSK (100kD)
phosphotyrosine immunoblot
transfected chick MuSK (140kD)
chick MuSK immunoblot
endogenous mouse MuSK (100kD)
mouse MuSK immunoblot

Fig.12.

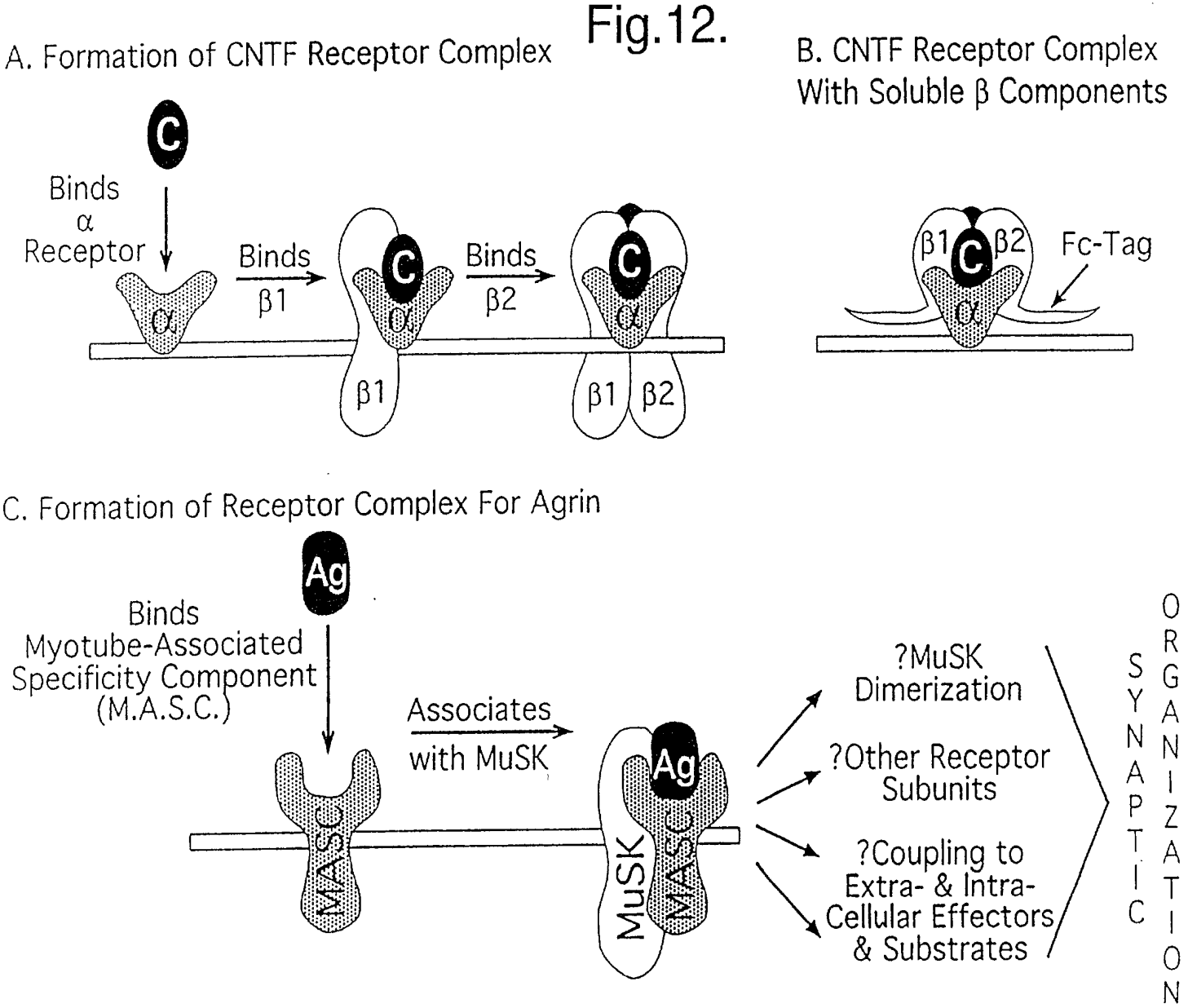

A. Formation of CNTF Receptor Complex
Binds α Receptor
Binds β1
Binds β2
C
α
β1
β2
B. CNTF Receptor Complex With Soluble β Components
Fc-Tag
C. Formation of Receptor Complex For Agrin
Ag
Binds Myotube-Associated Specificity Component (M.A.S.C.)
Associates with MuSK
MuSK
MASC
?MuSK Dimerization
?Other Receptor Subunits
?Coupling to Extra- & Intra-Cellular Effectors & Substrates
SYNAPTIC ORGANIZATION

Fig.13A.

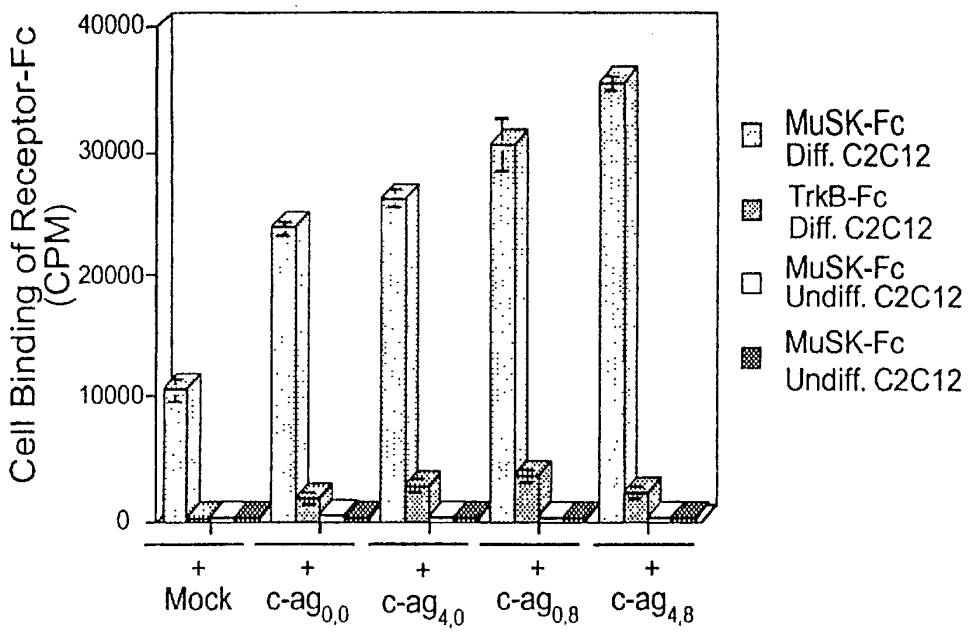


Fig.13B.

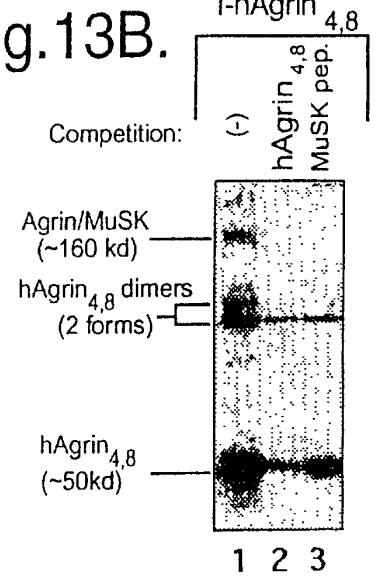


Fig.13C.

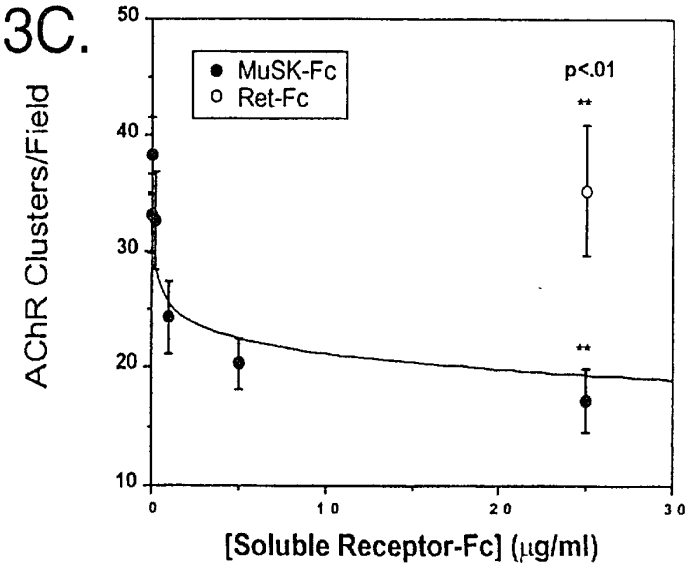


Fig. 14A

```
        10         20         30         40         50         60
MPPLPLEHRP RQEPGASMLV RYFMIPCNIC LILLATSTLG FAVLLFLSNY KPGIHFTPAP

        70         80         90        100        110        120
PTPPDVCRGM LCGFGAVCEP SVEDPGRASC VCKKNACPAT VAPVCGSDAS TYSNECELQR

       130        140        150        160        170        180
AQCNQQRRIR LLRQGPCGSR DPCANVTCSF GSTCVPSADG QTASCLCPTT CFGAPDGTVC

       190        200        210        220        230        240
GSDGVDYPSE CQLLSHACAS QEHIFKKFNG PCDPCQGSMS DLNHICRVNP RTRHPEMLLR

       250        260        270        280        290        300
PENCPAQHTP ICGDDGVTYE NDCVMSRIGA TRGLLLQKVR SGQCQTRDQC PETCQFNSVC

       310        320        330        340        350        360
LSRRGRPHCS CDRVTCDGSY RPVCAQDGHT YNNDCWRQQA ECRQQRAIPP KHQGPCDQTP

       370        380        390        400        410        420
SPCHGVQCAF GAVCTVKNGK AECECQRVCS GIYDPVCGSD GVTYGSVCEL ESMACTLGRE

       430        440        450        460        470        480
IQVARRGPCD PCGQCRFGSL CEVETGRCVC PSECVESAQP VCGSDGHTYA SECELHVHAC

       490        500        510        520        530        540
THQISLYVAS AGHCQTCGEK VCTFGAVCSA GQCVCPRCEH PPPGPVCGSD GVTYLSACEL

       550        560        570        580        590        600
REAACQQQVQ IEEAHAGPCE PAECGSGGSG SGEDDECEQE LCRQRGGIWD EDSEDGPCVC

       610        620        630        640        650        660
DFSCQSVPRS PVCGSDGVTY GTECDLKKAR CESQQELYVA AQGACRGPTL APLLPVAFPH

       670        680        690        700        710        720
CAQTPYGCCQ DNFTAAQGVG LAGCPSTCHC NPHGSYSGTC DPATGQCSCR PGVGGLRCDR

       730        740        750        760        770        780
CEPGFWNFRG IVTDGHSGCT PCSCDPRGAV RDDCEQMTGL CSCRPGVAGP KCGQCPDGQV

       790        800        810        820        830        840
LGHLGCEADP MTPVTCVEIH CEFGASCVEK AGFAQCICPT LTCPEANSTK VCGSDGVTYG
```

Fig. 14B

```
      850       860       870       880       890       900
      *  *      *  *      *  *      *  *      *  *      *  *
NECQLKAIAC RQRLDISTQS LGPCQESVTP GASPTSASMT TPRHILSKTL PFPHNSLPLS

      910       920       930       940       950       960
      *  *      *  *      *  *      *  *      *  *      *  *
PGSTTHDWPT PLPISPHTTV SIPRSTAWPV LTVPPTAAAS DVTSLATSIF SESGSANGSG

      970       980       990      1000      1010      1020
      *  *      *  *      *  *      *  *      *  *      *  *
DEELSGDEEA SGGGSGGLEP PVGSIVVTHG PPIERASCYN SPLGCCSDGK TPSLDSEGSN

     1030      1040      1050      1060      1070      1080
      *  *      *  *      *  *      *  *      *  *      *  *
CPATKAFQGV LELEGVEGQE LFYTPEMADP KSELFGETAR SIESTLDDLF RNSDVKKDFW

     1090      1100      1110      1120      1130      1140
      *  *      *  *      *  *      *  *      *  *      *  *
SVRLRELGPG KLVRAIVDVH FDPTTAFQAS DVGQALLRQI QVSRPWALAV RRPLQEHVRF

     1150      1160      1170      1180      1190      1200
      *  *      *  *      *  *      *  *      *  *      *  *
LDFDWFPTFF TGAATGTTAA MATARATTVS RLPASSVTPR VYPSHTSRPV GRTTAPPTTR

     1210      1220      1230      1240      1250      1260
      *  *      *  *      *  *      *  *      *  *      *  *
RPPTTATNMD RPRTPGHQQP SKSCDSQPCL HGGTCQDQDS GKGFTCSCTA GRGGSVCEKV

     1270      1280      1290      1300      1310      1320
      *  *      *  *      *  *      *  *      *  *      *  *
QPPSMPAFKG HSFLAFPTLR AYHTLRLALE FRALETEGLL LYNGNARGKD FLALALLDGR

     1330      1340      1350      1360      1370      1380
      *  *      *  *      *  *      *  *      *  *      *  *
VQFRFDTGSG PAVLTSLVPV EPGRWHRLEL SRHWRQGTLS VDGETPVVGE SPSGTDGLNL

     1390      1400      1410      1420      1430      1440
      *  *      *  *      *  *      *  *      *  *      *  *
DTNLYVGGIP EEQVAMVLDR TSVGVGLKGC IRMLDINNQQ LELSDWQRAA VQSSGVGECG

     1450      1460      1470      1480      1490      1500
      *  *      *  *      *  *      *  *      *  *      *  *
DHPCLPNPCH GGALCQALEA GMFLCQCPPG RFGPTCADEK SPCQPNPCHG AAPCRVLSSG

     1510      1520      1530      1540      1550      1560
      *  *      *  *      *  *      *  *      *  *      *  *
GAKCECPLGR SGTFCQTVLE TAGSRPFLAD FNGFSYLELK GLHTFERDLG EKMALEMVFL

     1570      1580      1590      1600      1610      1620
      *  *      *  *      *  *      *  *      *  *      *  *
ARGPSGLLLY NGQKTDGKGD FVSLALHNRH LEFCYDLGKG AAVIRSKEPI ALGTWVRVFL

     1630      1640      1650      1660      1670      1680
      *  *      *  *      *  *      *  *      *  *      *  *
ERNGRKGALQ VGDGPRVLGE SPKSRKVPHT MLNLKEPLYI GGAPDFSKLA RGAAVSSGFS
                        ▲
                        Y-site
```

Fig. 14C

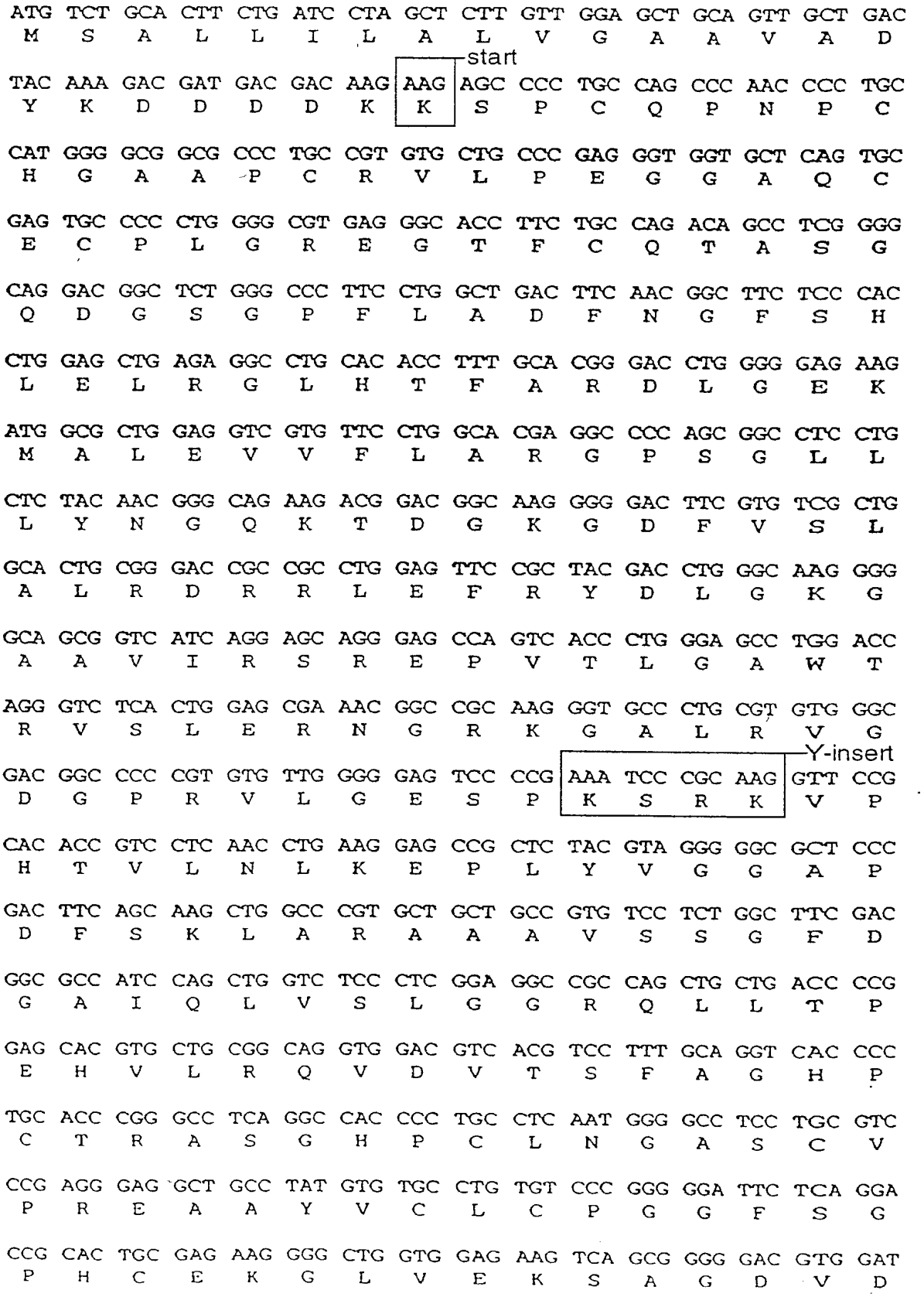
```
      1690        1700        1710        1720        1730        1740
    *   *   *   *   *   *   *   *   *   *   *   *
GVIQLVSLRG HQLLTQEHVL RAVDVSPFAD HPCTQALGNP CLNGGSCVPR EATYECLCPG

      1750        1760        1770        1780        1790        1800
    *   *   *   *   *   *   *   *   *   *   *   *
GFSGLHCEKG LVEKSVGDLE TLAFDGRTYI EYLNAVIESE KALQSNHFEL SLRTEATQGL
                                        ▲Z-site
      1810        1820        1830        1840        1850        1860
    *   *   *   *   *   *   *   *   *   *   *   *
VLWIGKAAER ADYMALAIVD GHLQLSYDLG SQPVVLRSTV KVNTNRWLRI RAHREHREGS

      1870        1880        1890        1900        1910        1920
    *   *   *   *   *   *   *   *   *   *   *   *
LQVGNEAPVT GSSPLGATQL DTDGALWLGG LQKLPVGQAL PKAYGTGFVG CLRDVVVGHR

      1930        1940
    *   *   *   *
QLHLLEDAVT KPELRPCPTP *
```

Fig. 15A

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 M   S   A   L   L   I   L   A   L   V   G   A   A   V   A   D

TAC AAA GAC GAT GAC GAC AAG AAG AGC CCC TGC CAG CCC AAC CCC TGC
 Y   K   D   D   D   D   K   K   S   P   C   Q   P   N   P   C

CAT GGG GCG GCG CCC TGC CGT GTG CTG CCC GAG GGT GGT GCT CAG TGC
 H   G   A   A   P   C   R   V   L   P   E   G   G   A   Q   C

GAG TGC CCC CTG GGG CGT GAG GGC ACC TTC TGC CAG ACA GCC TCG GGG
 E   C   P   L   G   R   E   G   T   F   C   Q   T   A   S   G

CAG GAC GGC TCT GGG CCC TTC CTG GCT GAC TTC AAC GGC TTC TCC CAC
 Q   D   G   S   G   P   F   L   A   D   F   N   G   F   S   H

CTG GAG CTG AGA GGC CTG CAC ACC TTT GCA CGG GAC CTG GGG GAG AAG
 L   E   L   R   G   L   H   T   F   A   R   D   L   G   E   K

ATG GCG CTG GAG GTC GTG TTC CTG GCA CGA GGC CCC AGC GGC CTC CTG
 M   A   L   E   V   V   F   L   A   R   G   P   S   G   L   L

CTC TAC AAC GGG CAG AAG ACG GAC GGC AAG GGG GAC TTC GTG TCG CTG
 L   Y   N   G   Q   K   T   D   G   K   G   D   F   V   S   L

GCA CTG CGG GAC CGC CGC CTG GAG TTC CGC TAC GAC CTG GGC AAG GGG
 A   L   R   D   R   R   L   E   F   R   Y   D   L   G   K   G

GCA GCG GTC ATC AGG AGC AGG GAG CCA GTC ACC CTG GGA GCC TGG ACC
 A   A   V   I   R   S   R   E   P   V   T   L   G   A   W   T

AGG GTC TCA CTG GAG CGA AAC GGC CGC AAG GGT GCC CTG CGT GTG GGC
 R   V   S   L   E   R   N   G   R   K   G   A   L   R   V   G

GAC GGC CCC CGT GTG TTG GGG GAG TCC CCG AAA TCC CGC AAG GTT CCG
 D   G   P   R   V   L   G   E   S   P   K   S   R   K   V   P

CAC ACC GTC CTC AAC CTG AAG GAG CCG CTC TAC GTA GGG GGC GCT CCC
 H   T   V   L   N   L   K   E   P   L   Y   V   G   G   A   P

GAC TTC AGC AAG CTG GCC CGT GCT GCT GCC GTG TCC TCT GGC TTC GAC
 D   F   S   K   L   A   R   A   A   A   V   S   S   G   F   D

GGC GCC ATC CAG CTG GTC TCC CTC GGA GGC CGC CAG CTG CTG ACC CCG
 G   A   I   Q   L   V   S   L   G   G   R   Q   L   L   T   P

GAG CAC GTG CTG CGG CAG GTG GAC GTC ACG TCC TTT GCA GGT CAC CCC
 E   H   V   L   R   Q   V   D   V   T   S   F   A   G   H   P

TGC ACC CGG GCC TCA GGC CAC CCC TGC CTC AAT GGG GCC TCC TGC GTC
 C   T   R   A   S   G   H   P   C   L   N   G   A   S   C   V

CCG AGG GAG GCT GCC TAT GTG TGC CTG TGT CCC GGG GGA TTC TCA GGA
 P   R   E   A   A   Y   V   C   L   C   P   G   G   F   S   G

CCG CAC TGC GAG AAG GGG CTG GTG GAG AAG TCA GCG GGG GAC GTG GAT
 P   H   C   E   K   G   L   V   E   K   S   A   G   D   V   D
```

Fig. 15B

```
ACC TTG GCC TTT GAC GGG CGG ACC TTT GTC GAG TAC CTC AAC GCT GTG
 T   L   A   F   D   G   R   T   F   V   E   Y   L   N   A   V

                                                        Z-insert
ACC GAG AGC GAA CTG GCC AAT GAG ATC CCC GTC GAG AAG GCA CTG CAG
 T   E   S   E   L   A   N   E   I   P   V   E   K   A   L   Q

AGC AAC CAC TTT GAA CTG AGC CTG CGC ACT GAG GCC ACG CAG GGG CTG
 S   N   H   F   E   L   S   L   R   T   E   A   T   Q   G   L

GTG CTC TGG AGT GGC AAG GCC ACG GAG CGG GCA GAC TAT GTG GCA CTG
 V   L   W   S   G   K   A   T   E   R   A   D   Y   V   A   L

GCC ATT GTG GAC GGG CAC CTG CAA CTG AGC TAC AAC CTG GGC TCC CAG
 A   I   V   D   G   H   L   Q   L   S   Y   N   L   G   S   Q

CCC GTG GTG CTG CGT TCC ACC GTG CCC GTC AAC ACC AAC CGC TGG TTG
 P   V   V   L   R   S   T   V   P   V   N   T   N   R   W   L

CGG GTC GTG GCA CAT AGG GAG CAG AGG GAA GGT TCC CTG CAG GTG GGC
 R   V   V   A   H   R   E   Q   R   E   G   S   L   Q   V   G

AAT GAG GCC CCT GTG ACC GGC TCC TCC CCG CTG GGC GCC ACG CAG CTG
 N   E   A   P   V   T   G   S   S   P   L   G   A   T   Q   L

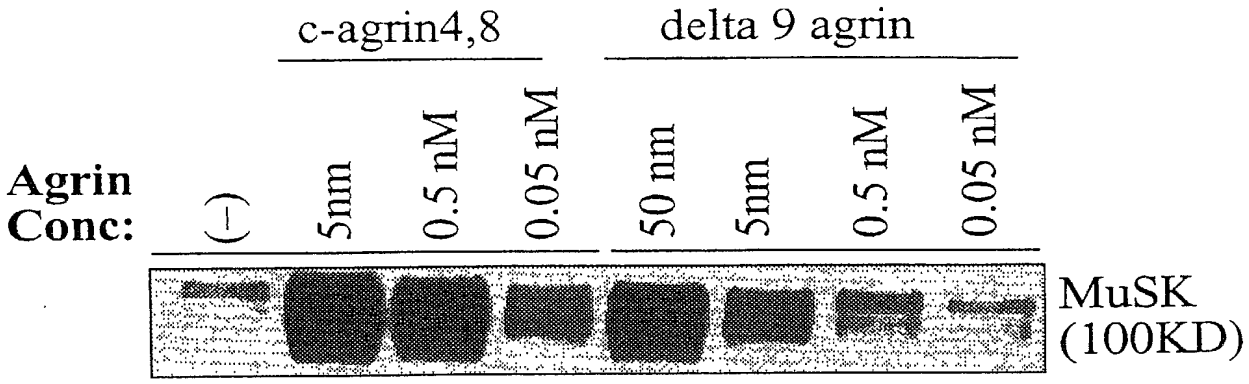
GAC ACT GAT GGA GCC CTG TGG CTT GGG GGC CTG CCG GAG CTG CCC GTG
 D   T   D   G   A   L   W   L   G   G   L   P   E   L   P   V

GGC CCA GCA CTG CCC AAG GCC TAC GGC ACA GGC TTT GTG GGC TGC TTG
 G   P   A   L   P   K   A   Y   G   T   G   F   V   G   C   L

CGG GAC GTG GTG GTG GGC CGG CAC CCG CTG CAC CTG CTG GAG GAC GCC
 R   D   V   V   V   G   R   H   P   L   H   L   L   E   D   A

GTC ACC AAG CCA GAG CTG CGG CCC TGC CCC ACC CCA TGA
 V   T   K   P   E   L   R   P   C   P   T   P   *
```

Fig.16.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delta 9 agrin
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(-)
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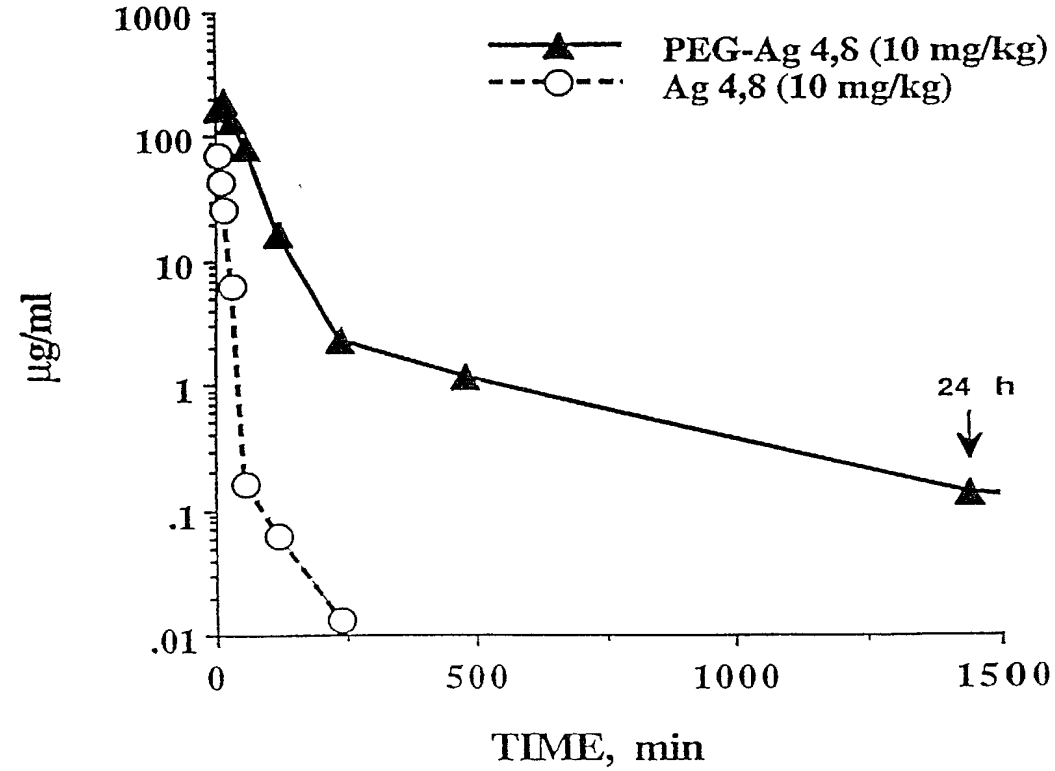
0.5 nM
0.05 nM
50 nm
5nm
0.5 nM
0.05 nM
MuSK (100KD)

Fig.17.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.1
.01
µg/ml
24 h
0
500
1000
1500
TIME, min